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Review Article

# Gut-Liver Axis: The Role of Intestinal Microbiota and Their Metabolites in the Progression of Metabolic Dysfunction-Associated Steatotic Liver Disease

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Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as one of the most prevalent chronic liver diseases globally, and its pathogenesis is closely linked to the imbalance of intestinal microbiota and their metabolites. This article reviews the mechanisms through which intestinal microbiota influence the progression of MASLD via the gut-liver axis, elaborating on the complex roles of immune cell hyperactivation, impaired intestinal barrier function, and intestinal microbial metabolites such as short-chain fatty acids and bile acids. The imbalance of intestinal microbiota not only directly promotes the development of MASLD but also further exacerbates disease progression through abnormalities in their metabolites. Various novel therapeutic strategies are being actively developed on the basis of gut-liver axis theory, including probiotic/prebiotic/synbiotic treatment, fecal microbiota transplantation, and targeted drug therapy. These strategies aim to precisely regulate microbial homeostasis and improve glucose and lipid metabolism, thereby alleviating hepatic inflammation and fibrosis and optimizing the therapeutic outcomes of patients with MASLD. In the future, as research progresses, we will further uncover the interaction mechanisms between intestinal microbiota and MASLD and continuously explore more effective treatment methods, with the goal of improving the prognosis and quality of life for MASLD patients. **(Gut Liver, 2025;19:479-507)**

**Key Words:** Non-alcoholic fatty liver disease; Gastrointestinal microbiome; Enterohepatic circulation; Metabolome; Therapeutics

## INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as an increasingly prominent global public health challenge.[1,2] As a ubiquitous chronic liver condition, MASLD is intricately associated with components of metabolic syndrome, including obesity, insulin resistance (IR), dyslipidemia, and abnormal blood pressure.[3] The core pathological feature of MASLD lies in the excessive accumulation of fat within the liver, a process independent of alcohol consumption that can further progress to severe liver pathology and even cancer.[4] With the acceleration of modern life pace and profound changes in dietary habits, the incidence of MASLD has soared to 25%, making it the leading cause of chronic liver disease worldwide.[5]

Recently, the exploration of the potential causal effects of the interaction between intestinal microbiota and the host in the pathogenesis of MASLD has become a research hotspot.[6] The intestinal microbiota and their metabolites exert profound influences on the initiation and progression of MASLD through the intricate regulatory network of the "gut-liver axis."[7] Serving as a crucial bridge connecting the intestine and liver, the gut-liver axis not only fulfills the basic physiological functions of nutrient absorption and waste excretion but also plays a pivotal role in regulating metabolic homeostasis, immune responses, and inflammatory reactions.[8]

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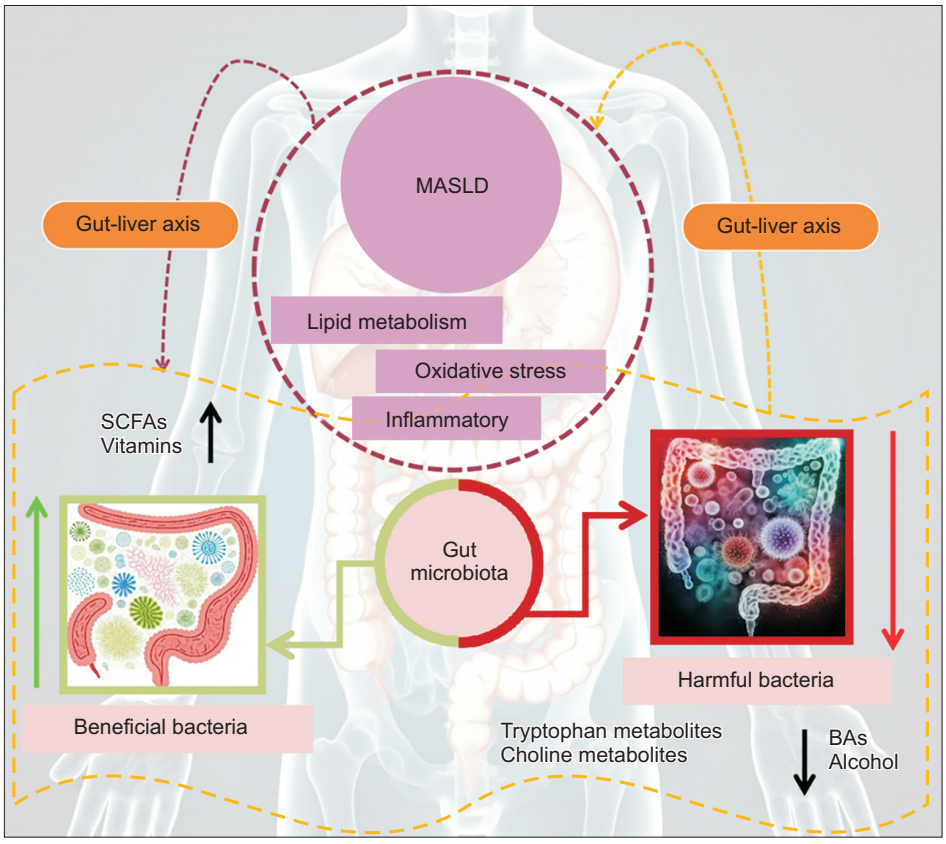


**Fig. 1.** Schematic diagram of the regulation of metabolic dysfunction-associated steatotic liver disease (MASLD) progression by gut microbiota and their metabolites through the gut-liver axis. SCFAs, short-chain fatty acids; BAs, bile acids.

This article aims to systematically review how intestinal microbiota and their metabolites precisely regulate the disease progression of MASLD through the complex gut-liver axis. We will delve into how alterations in the structure of intestinal microbiota, fluctuations in the abundance of specific bacterial populations, and the accumulation of their metabolites affect hepatic lipid metabolism, oxidative stress status, and inflammatory responses via the gut-liver axis, thereby promoting or inhibiting the development of MASLD (Fig. 1). Furthermore, this article will also provide insights into potential therapeutic strategies based on intestinal microbiota modulation, aiming to offer new ideas and directions for clinical intervention in MASLD and promote in-depth development in this research field.

## CONCEPT AND MECHANISM OF ACTION OF THE GUT-LIVER AXIS

The gut-liver axis, first proposed by Marshall in 1998, represents a complex and intricate physiological regulatory system. It describes the interactive network established between the gut (including its abundant microbiota) and the liver through biliary tracts, the portal vein, and systemic circulation.[9] This interactive process is jointly regulated by diet, genetic background, and environmental factors, forming mechanisms of material exchange, cellular communication, and cytokine-mediated mutual regulation and influence (Fig. 2).

### 1. Beneficial mechanisms of the gut-liver axis in MASLD

The gut-liver axis, as a pivotal physiological axis connecting the gut and liver, plays a crucial role in the initiation and progression of MASLD.[10] Research has revealed that gut commensal bacteria, particularly *Bacteroidetes*, significantly reduce hepatic lipid deposition by producing bacterial sphingolipids and transporting them to the liver via the gut-liver axis.[11] This mechanism operates primarily through two aspects.

Firstly, the intestinal barrier, serving as the first line of defense in the gut-liver axis, is crucial for maintaining liver health.[12] Functioning as a sophisticated biological barrier, it effectively prevents leakage of intestinal lumen microorganisms and their metabolites or potential toxins by ensuring the homeostasis of the gut microbiota, thereby creating a relatively sterile and stable internal environment for the liver. Restoration of its integrity also involves the repair of mucus, epithelial, and immune barriers.[13] When the intestinal barrier function is stable, it precisely regulates in-

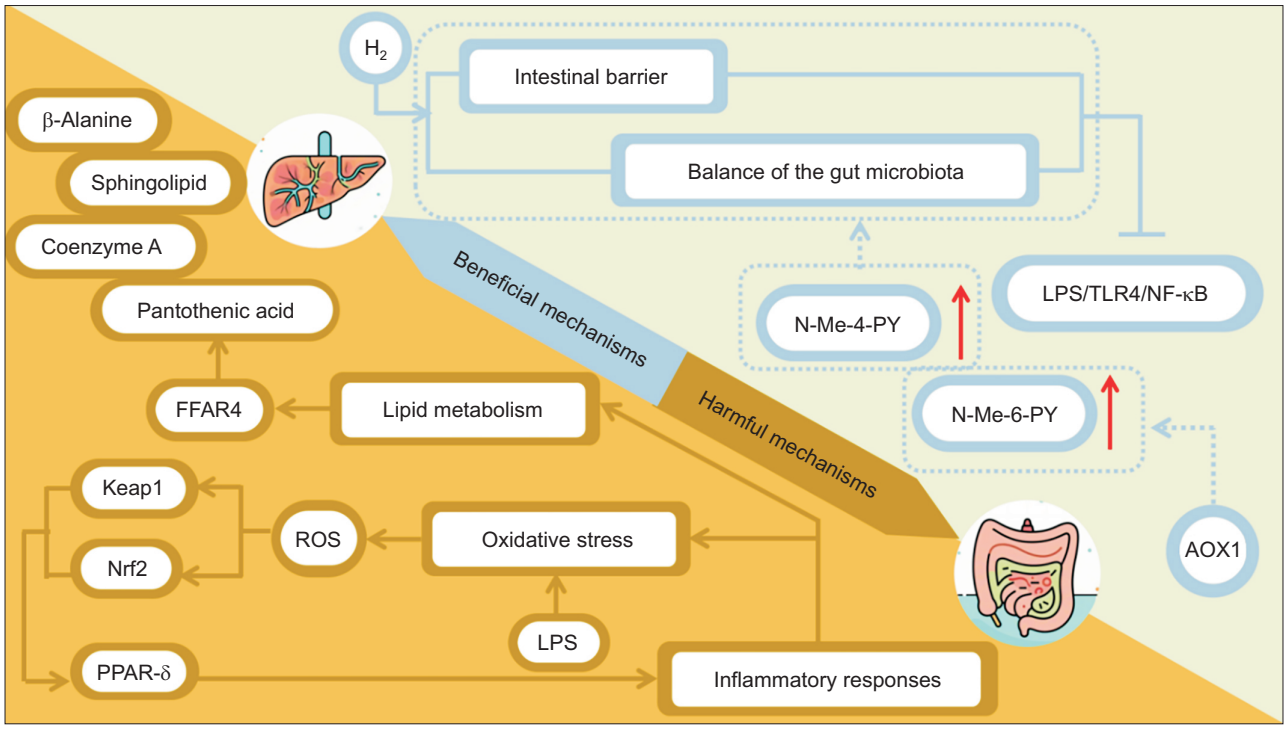


**Fig. 2.** Interaction mechanisms of the gut-liver axis. FFAR, free fatty acid receptor; Nrf2, nuclear factor E2-related factor 2; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; NF-κB, nuclear factor κB; N-Me-6-PY, N-methyl-6-pyridone-3-carboxamide; N-Me-4-PY, N-methyl-4-pyridone-5-carboxamide; AOX1, aldehyde oxidase 1.

testinal permeability, which helps reduce the risk of small intestinal bacterial overgrowth caused by factors such as reduced gastric acid and motility disorders.[14-16] This, in turn, strictly limits the abnormal transfer of microbial metabolites to the liver, thereby preventing the harmful effects of these substances on the liver. This is the primary mechanism for preventing and slowing the pathological progression of MASLD.[17] Furthermore, stable intestinal barrier function aids in maintaining the balance of the liver's immune microenvironment, appropriately responding to external stimuli and avoiding liver damage from excessive inflammatory responses, thereby slowing the pathological development of MASLD.[18]

Secondly, the balance of the gut microbiota has a decisive influence on the normal functioning of the gut-liver axis. Optimizing the composition and structure of the gut microbiota further promotes the stability of intestinal barrier function, prevents malabsorption disorders (such as those of vitamin $B_{12}$ [VB12], iron, choline, fats, carbohydrates, and proteins) and bile salt deconjugation, and indirectly affects hepatic lipid metabolism, oxidative stress, and inflammatory responses.[19] Metabolites of the gut microbiota, such as short-chain fatty acids (SCFAs), regulate hepatic lipid metabolism genes (Hmgcr, Srebp-1, Fasn, and Cyp7a1), thereby modulating the synthesis and oxidative decomposition of hepatic fatty acids and reducing excessive accumulation of liver fat.[20] They also regulate the oxidative stress status of the liver, mitigating damage to hepatocytes caused by oxidative stress. Additionally, the gut microbiota influences hepatic inflammatory responses by modulating immune reactions, effectively inhibiting the pathological progression of MASLD.[21] Research further confirms that the anti-MASLD effect of hydrogen inhalation is closely related to modulation of the gut microbiota, primarily through inhibition of the lipopolysaccharide (LPS)/Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) oxidative stress and inflammatory pathway.[22]

Notably, studies have also demonstrated that regulating gut microbiota remodeling and metabolic cofactors (such as betaine, N-acetylcysteine, L-carnitine, and nicotinamide riboside) can significantly improve high-fat diet (HFD)-induced MASLD in mice.[23] In particular, restoring N-methyl-6-pyridone-3-carboxamide and N-methyl-4-pyridone-5-carboxamide to normal levels due to upregulated aldehyde oxidase 1 has a significant effect on improving MASLD.[24] This discovery not only deepens our understanding of the mechanisms of action of the gut-liver axis in metabolic liver diseases but also provides new scientific evidence and potential therapeutic strategies for the prevention and treatment of MASLD.

### 2. Harmful mechanisms of the gut-liver axis in MASLD progression

The gut-liver axis, serving as a pivotal physiological axis connecting the intestine and liver, plays a crucial role in maintaining the homeostasis of the internal environment of the organism.[25] However, when the intestinal barrier function is compromised, this axis exerts profound adverse effects on the progression of MASLD. Specifically, the weakening of intestinal barrier function facilitates the crossing of intestinal microbiota and their metabolites, which then invade the liver through the portal venous system.[26] During this process, the hepatic immune system is abnormally activated, inducing or exacerbating hepatic inflammation, which becomes a core aspect of MASLD pathological progression. The overactivation of the immune system not only disrupts the balanced state of the intestinal microbiota, increases the burden on the liver, but also affects hepatic lipid metabolism, oxidative stress status, and inflammatory responses through a series of complex mechanisms, thereby promoting the progression of MASLD.

In terms of lipid metabolism, once the intestinal barrier function is impaired, lipids and their metabolites in the intestine more easily penetrate into the liver, exacerbating hepatic lipid deposition.[27] This not only aggravates the metabolic burden of the liver but may also further disrupt the balance of lipid metabolism in critical pathways such as pantothenic acid and coenzyme A biosynthesis, β-alanine metabolism, and sphingolipid metabolism by regulating the expression level of the lipid metabolism-related gene FFAR4 (free fatty acid receptor 4), thereby worsening the pathological condition of MASLD.[28] Regarding oxidative stress status, after the intestinal barrier function is compromised, harmful substances in the intestine, such as LPS and other bacterial components, more easily enter the liver through the portal venous system. The accumulation of LPS and other harmful substances in the liver can trigger oxidative stress reactions, generating a large amount of reactive oxygen species and regulating oxidative stress genes (e.g., Keap1 and Nrf2), leading to liver cell damage.[29] Meanwhile, oxidative stress reactions may further activate inflammatory responses and regulate inflammatory factors (e.g., peroxisome proliferator-activated receptor [PPAR]-δ), forming a vicious cycle that exacerbates MASLD progression.[30] In terms of inflammatory responses, after the intestinal barrier function is impaired, the hepatic immune system is overactivated, resulting in intensified hepatic inflammation. This inflammatory response not only directly damages liver cells but may also further affect hepatic lipid metabolism and oxidative stress status through mechanisms such as the release of inflammatory factors, thereby exacerbating the pathological process of MASLD.[31]

The harmful mechanisms of the gut-liver axis in MASLD progression primarily involve the invasion of the liver by microbiota and their metabolites due to impaired intestinal barrier function, overactivation of the immune system, and widespread effects on systemic metabolism. Further research has found that MASLD patients with intestinal barrier injury and increased intestinal permeability often have more severe disease states.[32] These patients exhibit further deterioration of liver dysfunction, including worsened hepatocyte damage, bile duct obstruction, and abnormal triglycerides (TG) metabolism. Serum D-lactate levels, as a sensitive marker for assessing increased intestinal permeability, show a significant positive correlation with indicators such as the degree of hepatocyte necrosis, bile duct obstruction, and abnormal TG metabolism in MASLD patients. Additionally, increased intestinal permeability (typically assessed by the lactulose/mannitol ratio) is also closely positively correlated with ethylemia, endotoxemia, and the degree of liver damage.[33] These findings further confirm the close link between impaired intestinal barrier function and MASLD progression.

## IMBALANCE OF GUT MICROBIOTA AND MASLD

The human gut microbiota primarily consists of the *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria phyla*, with *Bacteroidetes* and *Firmicutes* being dominant. The gut microbiota is closely associated with the regulation of human metabolism, immunity, and disease, and its imbalance is a crucial factor in the occurrence and progression of MASLD. Long-term unhealthy dietary habits, such as high-sugar diet and HFD and overeating, can induce ecological dysbiosis of the gut microbiota, subsequently leading to barrier function impairment and immune homeostasis disruption. The imbalance of gut microbiota may promote the development of MASLD through the following two mechanisms (Fig. 3).

### 1. Hyperactivation of immune cells

Imbalance in the gut microbiota, particularly alterations in the abundance of specific bacterial populations, exerts a significant influence on the progression of MASLD. In this process, excessive activation of immune cells plays a pivotal driving role.[34] The gut microbiota is capable of releasing a series of pro-inflammatory bioactive molecules, such as LPS,[35] which possess the ability to penetrate damaged intestinal barriers, subsequently activating intestinal luminal epithelial cells and macrophages within the liver,

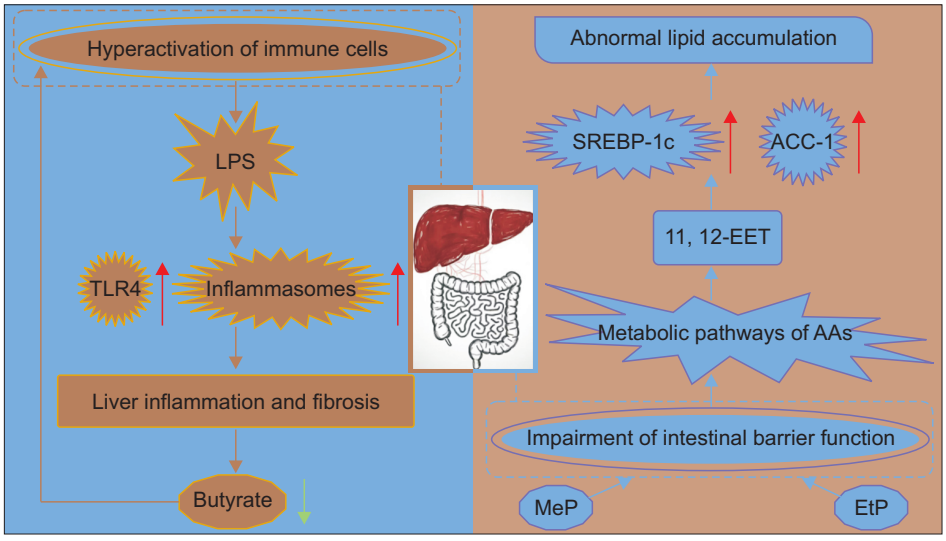


**Fig. 3.** Mechanisms of gut microbiota imbalance promoting metabolic dysfunction-associated steatotic liver disease development. LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; SREBP1, sterol regulatory element-binding protein 1; ACC-1, acetyl-CoA carboxylase 1; AAs, arachidonic acids; MeP, methylparaben; EtP, ethylparaben.

particularly Kupffer cells. This activation process induces the overexpression and release of inflammatory cytokines (e.g., tumor necrosis factors [TNF]-α, interleukin [IL]-1, IL-6), which not only exacerbates local inflammatory responses in hepatic tissue but may also lead to further liver injury, inflammation dissemination, and fibrotic development.[36] Specifically, LPS and other microbial derivatives promote the release of inflammatory cytokines by acting on intracellular signaling pathways in immune cells, such as TLR4 and inflammasomes, thereby initiating liver inflammation and fibrosis, and accelerating the pathological progression of MASLD.[37] Among them, TLR4 serves as the primary receptor for recognizing LPS. Binding of LPS to TLR4 triggers a cascade of downstream signaling events, ultimately leading to the activation of transcription factors such as NF-κB. Activation of NF-κB functions as the "master switch" for upregulation of inflammatory cytokine expression, facilitating the gene transcription and protein synthesis of TNF-α, IL-1, IL-6, and other inflammatory cytokines. The massive release of these inflammatory cytokines not only intensifies local inflammatory responses in hepatic tissue but may also cause direct hepatocyte damage, further promoting inflammation dissemination and fibrosis formation.

Beyond the TLR4 signaling pathway, inflammasome activation constitutes another crucial mechanism through which LPS and other microbial molecules exert their pro-inflammatory effects.[38] The inflammasome, a complex composed of multiple proteins, is responsible for recognizing and responding to intracellular stress signals, such as LPS. Upon inflammasome activation, it triggers a series of biochemical reactions, ultimately leading to the maturation and release of inflammatory cytokines such as IL-1β and IL-18. These inflammatory cytokines play pivotal roles in the processes of liver inflammation and fibrosis, capable of further recruiting and activating more immune cells, thereby forming a positive feedback loop that continually exacerbates pathological damage to the liver. Additionally, excessive activation of immune cells results in alterations in other inflammation-related biomarkers.[39] For instance, the expression levels of chemokines (e.g., C-X-C motif chemokine ligand 8, C-C motif chemokine ligand 2) and adhesion molecules (e.g., intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1) are significantly upregulated. These molecules play critical roles in the recruitment, migration, and infiltration of inflammatory cells, further promoting the progression of liver inflammation.

In MASLD patients, there is a significant correlation between gut microbiota imbalance and systemic inflammation. This imbalance is not only reflected in overall changes in microbiota structure but also specifically manifested in fluctuations in the abundance of specific bacterial groups, which profoundly impact the pathological progression of MASLD, particularly by promoting the hyperactivation of immune cells through the gut-liver axis mechanism. Specifically, studies have confirmed that the dominant *Prevotella copri* population is closely associated with a high risk of MASLD progressing to nonalcoholic steatohepatitis (NASH).[40] Increased abundance of *P. copri* may be related to elevated intestinal permeability and reduced butyrate production capacity. Increased intestinal permeability allows harmful substances within the intestine (such as bacteria and toxins) to more easily enter the bloodstream, triggering systemic inflammatory responses. Meanwhile, butyrate, an important SCFAs produced by gut microbial fermentation, has anti-inflammatory and immune-regulatory functions. The decline in its production further exacerbates immune system imbalance, promoting the

hyperactivation of immune cells.

Furthermore, in MASLD-hepatocellular carcinoma patients, enrichment of strains with unique microbiota/metabolome characteristics related to systemic inflammation and immune indicators has been observed.[41] Specifically, the increased abundance of potentially harmful microorganisms such as *Bacteroides* may accelerate the progression of disease. In contrast, members of the *Ruminococcaceae* family exhibit positive effects on maintaining intestinal health.[42] *Bacteroides* and other similar harmful microorganisms may exacerbate hepatic injury and inflammatory responses by secreting specific metabolites or directly modulating the function of intestinal immune cells. Conversely, members of the *Ruminococcaceae* family may have a beneficial impact on MASLD, contributing to the alleviation of disease conditions. Changes in gut microbiota community structure and fluctuations in the abundance of specific bacterial groups have significant impacts on the pathological progression of MASLD. These changes promote the hyperactivation of immune cells through the gut-liver axis mechanism, exacerbating systemic inflammatory responses and hepatocyte damage.[43] Therefore, a deep exploration of the relationship between gut microbiota imbalance and MASLD is of great significance for developing effective treatment strategies and preventing the progression of MASLD.

### 2. Impairment of intestinal barrier function

In the pathological progression of MASLD, the impairment of intestinal barrier function plays a central role, often initiating with an imbalance in the gut microbiota.[44] This imbalance can be triggered by various external factors, among which methylparaben and ethylparaben, as common food additive preservatives, are considered one of the key inducers.[45] These chemical substances interfere with the composition and function of the gut microbiota, affecting the metabolic pathways of arachidonic acids, leading to a reduction in important metabolites such as 11,12-epoxyeicosatrienoic acid. This not only disrupts the homeostasis of the intestinal microenvironment but also promotes abnormal expression of lipid metabolism-related genes (e.g., sterol regulatory element binding protein-1c and Acetyl-CoA Carboxylase 1) and proteins, accelerating abnormal lipid accumulation and thereby driving the development of MASLD.

On this basis, it is noteworthy that studies have shown significant sex-specific differences in the gut microbiome in MASLD. These differences are manifested not only in the composition of the microbiome but also in its functional characteristics.[46] Female rats exhibit higher β-diversity in the microbiome of both the jejunum and colon compared to male rats. This sex-specific imbalance in the microbiota may lead to distinct physiological and pathological responses. Specifically, male rats with MASLD show significantly elevated levels of LPS and TLR4 protein expression in the liver, which may directly reflect impaired intestinal barrier function and are closely associated with sex-specific changes in the microbiome. Therefore, sex-specific imbalance in the gut microbiota is considered an important factor influencing intestinal barrier function in the progression of MASLD.

The cascading effects of impaired intestinal barrier function are complex and profound.[47] Firstly, the regulatory mechanisms of metabolites produced by the gut microbiota become disrupted, with imbalances in the release of molecules such as LPS and SCFAs, while pathological changes such as ceramide fibrosis significantly intensify, severely compromising the integrity of the intestinal barrier. Furthermore, the compromised intestinal barrier permits the invasion of a large number of harmful substances, including LPS, peptidoglycan, bacterial DNA, and extracellular vesicles, into the circulatory system. These substances, acting as damage-associated molecular patterns and pathogen-associated molecular patterns, activate liver immune cells through receptors such as TLR4 and NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasomes, a member of the pattern recognition receptor family.[48] Notably, the activation of NLRP3 inflammasomes in MASLD triggers the production of inflammatory cytokines IL-1β and IL-18, further exacerbating the inflammatory response.[49]

In this process, the disrupted gut microbiota not only influences MASLD by altering its composition and metabolites but also leads to intestinal barrier injury through the gut-liver axis mechanism. This injury is not localized but also reduces the expression of intestinal tight junction protein ZO-1, increasing the translocation of intestinal-derived LPS to the liver, and subsequently activating the LPS/TLR4 and endoplasmic reticulum stress pathways.[50] These changes result in persistent inflammatory responses in the liver, exacerbating pathological states such as hepatocyte steatosis and inflammatory cell infiltration, and potentially accelerating the malignant transformation of MASLD to NASH. In particular, *Escherichia coli NF73-1* further disrupts the intestinal vascular barrier by inhibiting the Wnt/β-catenin signaling pathway, thereby exacerbating the progression of MASLD.[51] Therefore, targeting *E. coli NF73-1* or selectively enhancing interventions for intestinal vascular barrier dysfunction may represent effective potential approaches for the prevention and treatment of MASLD, helping to break the vicious cycle of inflammation triggered by the production of inflammatory cytokines resulting from intestinal barrier disruption.

## THE IMPACT OF GUT MICROBIOTA METABOLITES ON MASLD

Gut microbiota can produce a variety of metabolites that exert numerous effects, including altering host metabolism, immune function, and gene expression. The connection between gut microbiota metabolites and MASLD does not exist in isolation but rather constitutes a complex network involving interactions among multiple metabolic pathways, signaling molecules, and gene expressions. This discovery not only deepens our understanding of the pathogenesis of MASLD but also provides potential targets for the development of novel therapeutic strategies against this disease (Fig. 4).

### 1. Beneficial effects of gut microbiota metabolites on MASLD

#### 1) Short-chain fatty acids

SCFAs are transported to the liver through the portal venous circulation, and some enter the systemic circulation via the inferior vena cava, participating in the regulation of whole-body metabolism. Due to normal gut-liver axis function, SCFAs play significant roles in both intestinal and hepatic tissues, further highlighting their beneficial effects on MASLD. As important metabolites of gut microbiota, SCFAs exert a positive influence on the development of MASLD by modulating intestinal immunity and metabolism and directly acting on hepatic metabolic pathways. Notably, studies have confirmed that elevated SCFAs concentrations are closely associated with the immunological characteristics of MASLD progression.[52] This suggests that increasing the production and/or intake of SCFAs in the gut may emerge as an effective therapeutic strategy for MASLD. SCFAs, including butyrate, are key products of gut microbiota fermentation of indigestible carbohydrates such as dietary fiber.[53] These metabolites exhibit remarkable beneficial effects in the pathogenesis of MASLD.[54]

SCFAs not only provide an energy source for the host but also exert significant impacts on the development of MASLD by regulating intestinal immunity and metabolism. Specifically, SCFAs enhance insulin sensitivity and reduce inflammation, thereby lowering the risk of MASLD occurrence. This mechanism may involve the regulation of gut microbiota communities by SCFAs and the maintenance of intestinal barrier integrity. Notably, butyrate, as a crucial component of SCFAs, demonstrates a significant protective effect on MASLD.[55] One of its mechanisms is that butyrate potently promotes the differentiation of

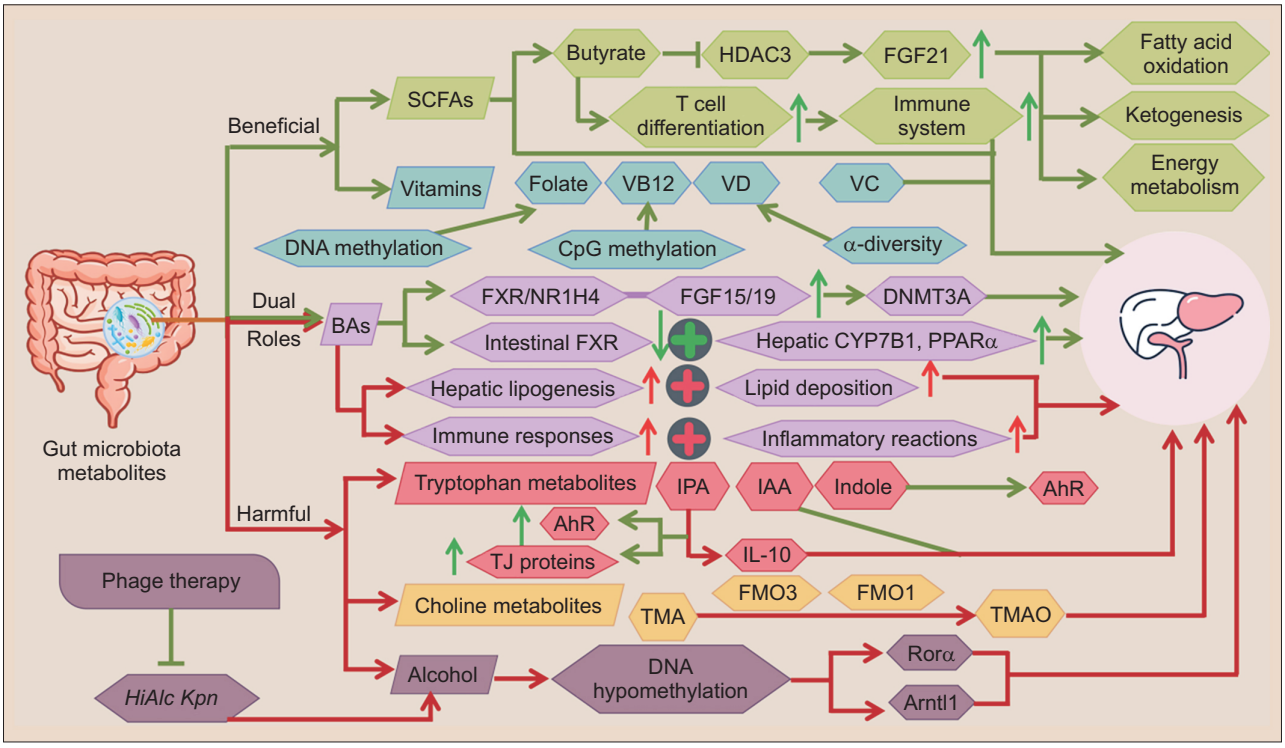


**Fig. 4.** The complex network relationship between gut microbiota metabolites and metabolic dysfunction-associated steatotic liver disease. SCFAs, short-chain fatty acids; HDAC3, histone deacetylases; FGF, fibroblast growth factor; VB12, vitamin $B_{12}$; VD, vitamin D; VC, vitamin C; BAs, bile acids; FXR, farnesoid X receptor; NR1H4, nuclear receptor subfamily 1 group H member 4; DNMT3A, DNA methyltransferase 3 alpha; PPAR, peroxisome proliferator-activated receptor; IPA, indole-3-propionic acid; IAA, indole acetic acid; AhR, aryl hydrocarbon receptor; TJ, tight junction; IL, interleukin; TMA, trimethylamine; FMO, flavin-containing monooxygenase 3; TMAO, trimethylamine oxide.

regulatory T cells, a process closely linked to fatty acid oxidation pathways. Specifically, butyrate optimizes the efficiency of fatty acid oxidation by regulating the intracellular metabolic environment, providing appropriate energy and material substrates for T cell differentiation. This enhanced differentiation subsequently helps regulate immune system homeostasis and alleviate immunopathological damage to the liver, thereby exhibiting a significant protective effect on MASLD. This finding offers a new perspective on understanding the role of butyrate in the pathogenesis of MASLD and provides potential targets for developing therapeutic strategies against MASLD.

Moreover, SCFAs control the expression of genes related to hepatic lipid metabolism through epigenetic mechanisms, thereby regulating the lipid metabolic process in the liver. This mechanism involves the inhibition of histone deacetylases (HDACs), particularly HDAC3, within the liver cell nucleus by SCFAs. Animal studies have found that butyrate, as one of the main components of SCFAs, significantly inhibits HDAC3 activity in the livers of diet-induced obese C57BL/6J mice.[56] This inhibition promotes the gene expression of fibroblast growth factor 21 (FGF21), which then mediates the biological activity of butyrate. As an important metabolic regulator, FGF21 plays a crucial role in regulating fatty acid oxidation, ketogenesis, and energy metabolism.[57] By increasing fatty acid utilization and promoting the occurrence of ketosis, FGF21 improves hepatic lipid deposition and IR, thereby benefiting the treatment of MASLD.[58] Therefore, butyrate further enhances its beneficial effects on MASLD by promoting the expression of FGF21.

### 2) Vitamins

Despite the introduction of new terms such as MASLD to more comprehensively describe liver diseases associated with metabolic dysfunction, emphasizing the significance of metabolic factors, the precise contributions of metabolic dysfunction, alcohol consumption, and other factors to the development and progression of liver diseases remain unclear.[59] This background information is crucial for understanding the potential beneficial effects of gut microbiota metabolites, particularly vitamins, in the progression of MASLD, as the interaction between metabolic factors and the gut microbiota may be one of the key factors influencing liver disease progression. In this context, vitamins, particularly vitamin $B_9$ (folate), VB12, and vitamin D, serve as significant metabolites of or are influenced by the gut microbiota, exerting notable beneficial effects in the pathophysiological processes of MASLD. Meanwhile, vitamin C, as an essential exogenous nutrient, also demonstrates a positive role in the treatment and prevention of MASLD. These vitamins impact the gut-liver axis through intricate mechanisms, thereby modulating the progression of MASLD, such as gut microbiota dysbiosis, hepatic lipotoxicity, immune system alterations, inflammatory responses, and oxidative stress.

Folate, as the core methyl donor, is deeply involved in one-carbon metabolism, providing necessary methyl groups for DNA methylation. Folate not only regulates the composition and function of the gut microbiota but also indirectly influences the development of MASLD by optimizing the intestinal microenvironment.[60] Studies indicate that inadequate folate levels are an independent predictor of histological severity in MASLD patients with NASH, and its dysregulation may promote the occurrence and progression of MASLD by modulating DNA methylation status. In mouse experiments, a diet lacking methyl groups led to hypomethylation of multiple genes on CpG islands, further confirming the crucial role of folate in MASLD pathophysiology. Additionally, dietary methyl donor supplements, including folate, can effectively protect rodents from diet-induced hepatic steatosis by reversing the methylation status of genes involved in lipid metabolism (Fas, Atgl, Hsl, Ppar-α, adiponectin, resistin, and Ucp2).[61]

VB12 also has a significant impact on the pathophysiological processes of MASLD. VB12 facilitates the biosynthesis of methyl groups. Research shows that, in mouse experiments, oral VB12 caused CpG methylation differences in genes related to intestinal barrier function, fatty acid metabolism, and mitochondrial metabolism, while inhibiting inflammatory responses.[62] This discovery reveals that VB12 may improve MASLD-related pathophysiological processes by regulating gene methylation status. Therefore, VB12 supplementation has the potential to become a therapeutic strategy for MASLD.

Furthermore, vitamin D treatment can effectively alleviate symptoms and liver function damage induced by HFD in MASLD by restoring gut microbiota balance (specifically manifested as a decreased *Firmicutes*/*Bacteroidetes* ratio but increased α-diversity, increased abundance of *Prevotella* and *Porphyromonadaceae*, and reduced abundance of harmful bacteria) and improving metabolism (enhanced biosynthesis of tyrosine, tryptophan, and arginine, sphingolipid metabolism, and positive correlation with various beneficial metabolites).[63] Notably, vitamin C and vitamin $D_3$ exhibit similar and synergistic mechanisms in the treatment of MASLD. They contribute to mitigating the pathophysiological process of MASLD by modulating the gut microbiota, improving intestinal barrier integrity, regulating bile acids (BAs) metabolism (inhibiting apical sodium-dependent BA transporter activity and activating 7α-hydroxylase [CYP7A1], farnesoid X receptor [FXR], and bile salt export pump), and reducing oxidative stress

and inflammation in the gut-liver axis.[64]

## 2. Harmful effects of gut microbiota metabolites on MASLD

### 1) Tryptophan metabolites

In exploring the complex and profound impacts of gut microbiota metabolites on MASLD, tryptophan metabolites, as a class of key microbially derived compounds, have gradually emerged as significant promoters of MASLD pathological processes, attracting widespread attention in the academic community.[65] Studies have revealed that upregulation of the tryptophan-kynurenine-aryl hydrocarbon receptor (AHR) signaling axis in the liver may be closely associated with the intensification of hepatic steatosis and severe imbalances in glucose and lipid metabolism during MASLD progression.[66] Tryptophan, a crucial product of dietary protein digestion, is further converted into various biologically active metabolites, including but not limited to indole-3-propionic acid (IPA), indole acetic acid (IAA), and indole, by tryptophanases catalyzed by intestinal flora.[67] These metabolites serve as important signaling mediators within microbial communities and between them and the host, exerting significant influences on MASLD development through a series of finely regulated biological mechanisms.

Tryptophan metabolites, particularly IPA, exert a crucial impact on the pathological progression of MASLD through the gut-liver axis, a complex network system connecting the intestine and liver. In the intestine, commensal bacteria produce indole-like metabolites such as IPA through deamination, which activate Aryl Hydrocarbon Receptor, promote the proliferation and differentiation of intestinal epithelial cells, enhance intestinal barrier function by stimulating the expression of tight junction proteins, and inhibit the permeation of toxic factors.[68] However, they may also interfere with the normal immune homeostasis between the intestine and liver by downregulating the expression of the anti-inflammatory cytokine IL-10, leading to liver inflammation and steatosis, thereby accelerating MASLD progression. Despite the anti-inflammatory and antioxidant effects of IPA, its overall effect may promote disease progression in the context of MASLD pathology.

Notably, IAA, another important product of tryptophan metabolism, exhibits a more complex dual impact on MASLD.[69] On the one hand, IAA acts on macrophages and hepatocytes to reduce hepatic lipogenesis, oxidation, and inflammatory stress, demonstrating a certain protective effect against liver injury in MASLD mice induced by an HFD. However, on the other hand, this protective effect of IAA is not absolute, and its actual effect is constrained by various factors, including metabolite concentration, duration of action, individual differences, and interactions with other metabolites. These factors collectively determine the specific mode of action and effect of IAA in MASLD pathology.

Nevertheless, indole, as a key product of tryptophan metabolism by gut microbiota, demonstrates remarkable anti-inflammatory and antioxidant properties. Recent research focusing on the role of indole in HFD-induced MASLD has revealed its positive impact on MASLD through a specific mechanism, namely the angiotensin-converting enzyme 2 (ACE2)-dependent pathway.[70] Indole significantly improves the degree of hepatic steatosis, alleviates inflammatory responses, and regulates the levels of Ang-(1-7) and the expression of ACE2 in serum, while maintaining mitochondrial function, making it an effective approach for the prevention and treatment of MASLD.

### 2) Choline metabolites

The dysregulation of choline metabolism is closely associated with the development of MASLD.[71] Under the condition of intestinal microbiota imbalance, the abnormal accumulation of choline and its metabolites significantly disrupts the balance of choline metabolism, thereby promoting the occurrence of MASLD. Specifically, intestinal microbiota metabolize choline and carnitine from the diet, producing trimethylamine (TMA). Subsequently, TMA is taken up by the liver and further metabolized into TMA oxide (TMAO) under the catalysis of FMO3 and FMO1.[72] Choline metabolites produced by intestinal microbiota, such as TMA and TMAO, are transported to the liver through the gut-liver axis, triggering a series of metabolic and inflammatory responses in the liver.[73] These responses not only exacerbate hepatic steatosis but also promote the progression of MASLD.

Studies have shown that TMAO, as a key intestinal microbiota metabolite, exerts harmful effects on MASLD through the gut-liver axis.[74] On the one hand, TMAO exacerbates the disruption of the intestinal barrier, leading to increased intestinal permeability and thus facilitating the leakage of harmful substances from the intestine. On the other hand, TMAO activates the TLR4/MyD88 (myeloid differentiation primary response 88)/NF-κB signaling pathway and inhibits the WNT/β-catenin pathway, thereby initiating inflammatory responses and fibrotic processes in the liver. Furthermore, research has confirmed that TMAO can directly induce different pathological states of MASLD in zebrafish livers, with the activation of the protein kinase R-like endoplasmic reticulum kinase pathway being a key mechanism.[75] However, recent studies have demonstrated that the ingestion of TMAO improves liver injury in FXR-deficient mice, further altering BAs/cholesterol metabo-

lism in an FXR-independent manner.[76]

TMA and/or TMAO, as novel biomarkers of early metabolic syndrome, are closely related to the severity of MASLD. Clinical studies have revealed that TMAO levels are significantly elevated in patients with more severe MASLD, while betaine levels and the betaine/choline ratio exhibit a downward trend.[77] This finding further supports the crucial role of choline metabolites in the development of MASLD. To gain a deeper understanding of the impact of choline metabolites on MASLD, researchers have also conducted animal experiments. In a mouse model induced by a choline-deficient diet, typical pathological features of MASLD were observed, which were not limited to a significant increase in hepatic fat content but also accompanied by significant changes in the structure of intestinal microbiota communities. More seriously, the model mice also exhibited signs of liver fibrosis, an important marker of the progression of MASLD to more severe stages.[78] Additionally, experimental results showed a significant correlation between increased TMA and TMAO levels and exacerbated MASLD, which was mainly mediated through the activation of unfolded protein response-related proteins GRP78, XBP1, and Derlin-1.[79]

The gut-liver axis, as an important channel connecting the intestine and liver, plays a crucial role in this process. It is worth mentioning that TMAO may also modify genes related to MASLD through epigenetic mechanisms. Studies have shown that TMAO upregulates the expression of members of the miR-17/92 cluster in the liver and increases the expression of target genes (serpin peptidase inhibitor, clade E [nexin, plasminogen activator inhibitor type 1], member 1 and IL-12A) associated with atherosclerosis and inflammation.[80] Furthermore, TMAO can promote the occurrence and accelerate the progression of MASLD by regulating the expression levels of miR-34a and miR-122.[81] These findings further reveal the complexity and diversity of choline metabolites in the pathogenesis of MASLD.

### 3) Alcohol

In addition to nonalcoholic factors, the progression of cirrhosis and its complications is closely related to specific changes in the gut microbiota and their metabolites. Studies have shown that certain bacteria in the gut microbiota, such as high-alcohol-producing *HiAlc Kpn*, are capable of generating substantial amounts of alcohol during their metabolic processes. The accumulation of this metabolite exerts significant detrimental effects on the pathological progression of MASLD.[82] Alcohol metabolized by *HiAlc Kpn* in the gut is transported to the liver through the complex physiological mechanism of the gut-liver axis, exerting direct toxic effects on hepatocytes and thereby promoting the development of MASLD.

The gut-liver axis serves as a crucial bridge connecting the gut and the liver, participating not only in the absorption and metabolism of nutrients but also playing a central role in the transport of pathogens and their metabolites. The accumulation of alcohol metabolites induced by *HiAlc Kpn*, upon entering the liver through the gut-liver axis, can trigger a series of pathological changes. These changes include abnormal expression of cytokines, leading to exacerbated inflammatory responses and significantly elevated cytokine levels, further intensifying liver injury. Additionally, alcohol metabolites activate the expression of lipogenic genes, promoting the production and accumulation of fat in the liver, thereby contributing to the formation of fatty liver.

It is noteworthy that *HiAlc Kpn*-induced liver injury is closely associated with DNA hypomethylation.[83] DNA hypomethylation, as an important epigenetic modification, regulates gene expression patterns and subsequently affects the normal physiological functions of cells. In *HiAlc Kpn*-induced MASLD models, DNA hypomethylation modulates the expression of genes related to lipid formation and circadian rhythm signaling pathways (such as Rorα and Arntl1 genes). The abnormal changes in the expression of these genes further exacerbate lipid metabolism disorders and DNA damage, thereby accelerating the occurrence and development of MASLD.

Furthermore, studies have shown that patients with liver cirrhosis exhibit unique characteristics of the intestinal microbiota, such as an increase in *Veillonella* bacteria and *Ruminococcus gnavus*, along with significant alterations in the metabolite profile. These changes are not only associated with complications of liver cirrhosis (including varices, ascites, and encephalopathy), but also highlight the crucial role of the intestinal microbiota and metabolites in the progression of nonalcoholic fatty liver disease.[84] Particularly, under the influence of external factors such as alcohol, changes in intestinal microbial metabolites further exacerbate the detrimental effects of liver cirrhosis, rendering research in this field more in-depth and complex.

Phage therapy has demonstrated potential therapeutic potential for *HiAlc Kpn*-induced MASLD.[85] By specifically targeting *HiAlc Kpn*, phage therapy can effectively alleviate the steatohepatitis caused by it, including improving liver dysfunction, reducing cytokine levels, and inhibiting the expression of lipogenic genes. This treatment approach not only reduces the production and accumulation of alcohol metabolites but also regulates inflammation, lipid, and carbohydrate metabolism in the liver, thereby achieving effective intervention in MASLD.

### 3. The dual roles of BAs in MASLD

BAs, as crucial bioactive substances released by the liver into the intestine through the biliary system, play pivotal roles in lipid metabolism and inflammatory responses, influencing the pathological progression of MASLD.[86] Specifically, the detrimental effects of BAs on MASLD are manifested in several ways: first, abnormal BAs metabolism may promote hepatic lipogenesis, exacerbating lipid deposition in the liver; second, by modulating immune responses, BAs may intensify hepatic inflammatory reactions, further driving MASLD towards more severe pathological stages such as NASH and fibrosis.

With the involvement of the gut microbiota, primary BAs are converted into secondary BAs, a process vital for the bioactivity and functions of BAs. However, when the gut microbiota is imbalanced, the proportion of BAs metabolites may be disturbed, which can not only interfere with the integrity of intestinal barrier function but also disrupt the homeostasis of energy metabolism, thereby accelerating the development of MASLD.[87] This interaction between the gut and liver constitutes one of the core mechanisms of the gut-liver axis. Among them, a group of BAs modified by the gut microbiota, hyodeoxycholic acid, is negatively correlated with MASLD and exhibits potential for MASLD treatment through mechanisms such as inhibiting intestinal FXR, upregulating hepatic CYP7B1 and PPAR-α, and increasing the abundance of probiotics. These effects complement the complex signaling pathways mediated by BAs and their metabolites through nuclear receptors and G protein-coupled receptors (such as Takeda G protein-coupled receptor 5, also known as G protein-coupled BAs receptor 1), which finely regulate lipid and glucose homeostasis and immune responses.[88,89]

Furthermore, both animal and human studies have shown that BAs can also regulate the expression of lipid metabolism-related genes through epigenetic mechanisms, thereby influencing the progression of MASLD. For example, BAs can induce the activation of the FGF15/19 signaling pathway through FXR/nuclear receptor subfamily 1 group H member 4, subsequently recruiting DNA methyltransferase 3 alpha to lipogenic genes and inhibiting hepatic lipogenesis through DNA methylation.[90] Additionally, secondary BAs such as taurine-α-muricholate can reshape histone modifications around specific genes, leading to their downregulation and thereby improving developmental programmed hepatic steatosis.[91]

## THERAPEUTIC STRATEGIES

Emerging novel therapeutic strategies targeting the role of the gut microbiota and its metabolites in MASLD, based on the gut-liver axis theory, encompass probiotics/prebiotics/synbiotics therapy, fecal microbiota transplantation (FMT) technology, and targeted medications. These aim to precisely regulate microbial homeostasis, modulate glucose and lipid metabolism, alleviate hepatic inflammation and fibrosis, and optimize the treatment outcomes for MASLD.

### 1. Probiotics/prebiotics/synbiotics therapy

MASLD represents a global health issue, with intestinal microbiota playing a pivotal role in its pathogenesis.[92] In recent years, probiotics, prebiotics, and their synthetic formulations targeting the gut microbiota have emerged as research hotspots in the field of MASLD treatment. By scientifically and rationally supplementing probiotics, prebiotics, or synbiotics (i.e., combinations of probiotics and prebiotics), it is feasible to effectively regulate the composi-

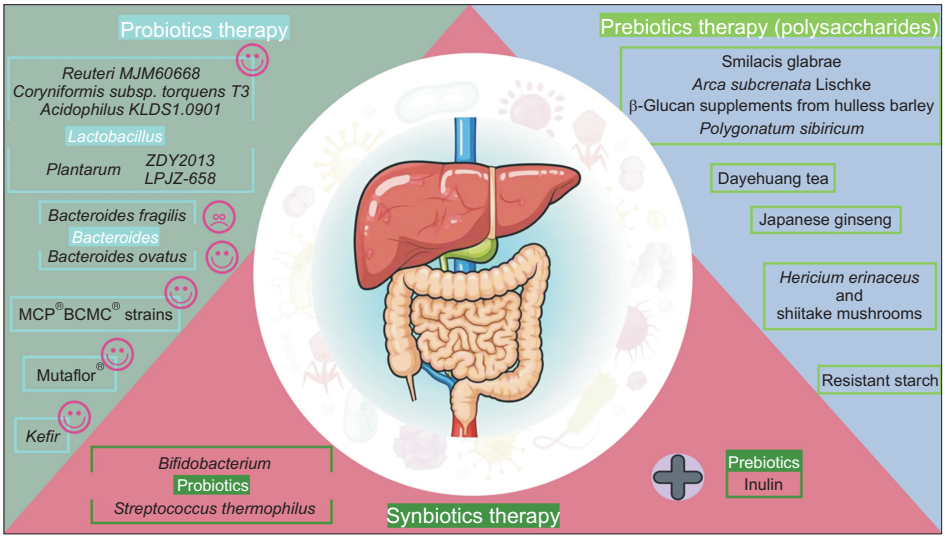


**Fig. 5.** The emerging role of probiotics, prebiotics, and synthetic formulations in the treatment of metabolic dysfunction-associated steatotic liver disease .

tion and metabolic activities of the gut microbiota. Simultaneously, this approach can reduce hepatic fat content, histological steatosis, and fibrosis. Furthermore, it effectively lowers the levels of inflammatory cytokines, thereby significantly improving intestinal barrier function and optimizing immune homeostasis. This provides novel strategies and approaches for the treatment of MASLD (Fig. 5). Despite their promising prospects and demonstrated potential in treating MASLD, further research is required to fully understand their mechanisms of action and optimize efficacy. Future studies should explore personalized treatment strategies, incorporating microbiota characteristics, blood metabolites, and customized dietary interventions, to enhance treatment effectiveness. The implementation of these personalized strategies is expected to further enhance the therapeutic efficacy of probiotics, prebiotics, and synbiotics in the treatment of MASLD.

### 1) Probiotics

An increasing number of studies have investigated the use of probiotics in the prevention and treatment of MASLD.[93] As a potential probiotic, *Bacteroides* can significantly ameliorate the pathological progression of MASLD by modulating gut microbiota composition, enhancing gut-liver folate metabolism, and unsaturated fatty acid metabolism.[94] However, different species of *Bacteroides* exhibit varied effects on MASLD. For instance, commensal *Bacteroides fragilis* exacerbates MASLD in mice fed a HFD, primarily by disrupting lipid metabolism, increasing harmful gut bacteria and endotoxin levels, and leading to glucose and lipid metabolic disorders.[95] In contrast, *Bacteroides ovatus* effectively alleviates MASLD induced by high-fat and high-cholesterol diets by optimizing gut microbiota diversity, increasing fecal SCFAs, reducing inflammatory cytokine levels (such as LPS, CD163, IL-1β, TNF-α), and regulating genes related to fat metabolism.[96]

*Lactobacillus reuteri MJM60668* effectively prevents the progression of MASLD by inhibiting lipogenesis (decreasing the expression of acetyl-CoA carboxylase, fatty acid synthase, sterol regulatory element-binding protein), promoting fatty acid oxidation (increasing the expression of PPAR-α, carnitine palmitoyltransferase), reducing inflammation levels (decreasing serum IL-1β levels and increasing adiponectin), and improving the gut microbiota (increasing the proportions of *Akkermansiaceae* and *Lachnospiraceae*). These benefits are associated with reduced liver weight, decreased liver/body weight ratio, improved liver function indicators (alanine aminotransferase [ALT], aspartate aminotransferase [AST], TG, total cholesterol [TC]), enhanced mucus barrier, and lowered TG levels.[97] Additionally, *Lactobacillus coryniformis* subsp. *torquens T3* and *Lactobacillus acidophilus KLDS1.0901* can also mitigate MASLD by reconstructing the gut microbiota and redox system.[98,99] *Lactobacillus plantarum ZDY2013* and *LPJZ-658* effectively inhibit the development of MASLD induced by high-fat, high-fructose, high-cholesterol, or copper deficiency combined with high-sugar diets by modulating the gut microbiota and various metabolic pathways (including inhibiting the LPS/NF-κB pathway, improving IR, regulating the PI3K/Akt pathway, lipid metabolism, and serum metabolites), avoiding folate and choline deficiency, significantly reducing hepatic steatosis, and restoring liver function.[100,101]

Beyond *Bacteroides* and *Lactobacillus*, MCPBCMC strains and Mutaflor are also effective in the prevention and treatment of MASLD/NASH. MCPBCMC strains positively impact liver health by stabilizing gut mucosal immune function and improving mucosal permeability.[102] Mutaflor slows the progression of MASLD/NASH by modulating the genetic-epigenetic network associated with hepatic stellate cell (HSC) signaling pathways (inhibiting hedgehog and hippo pathways, reducing the expression of HSC activation and profibrotic cytokine IL-6 and transforming growth factor-β effector proteins, while downregulating the expression of miR-650, Forkhead Box Protein A2, and TEA domain transcription factor 2, and upregulating the expression of large tumor suppressor homolog 2 [Drosophila]).[103] Furthermore, *kefir*, known as the "king of natural probiotics," also exhibits protective effects against MASLD.[104]

### 2) Prebiotics

Prebiotics, as substances capable of selectively promoting the growth of beneficial bacteria in the gut, have demonstrated significant potential in the treatment of MASLD.[105] By precisely modulating the gut microbiota structure, prebiotics effectively inhibit bile salt hydrolase-producing bacteria, promote taurine-metabolizing bacteria, and closely interact with microbial genera strongly associated with specific bile acid monomers, thereby optimizing the composition of colonic bile acids, elevating the levels of conjugated bile acids and non-12-OH BAs, and facilitating bile acid synthesis and excretion. This series of processes may further regulate the enterohepatic circulation by activating the hepatic FXR-hepatic portal (FXR-HP) pathway, influencing the expression of related proteins such as FXR and FGF15, ultimately effectively preventing the occurrence and progression of MASLD.

As a natural polymeric substance with exceptional prebiotic properties, polysaccharide from Dayehuang tea exhibits significant efficacy in MASLD.[106] It not only regulates the gut microbiota structure but also optimizes the

composition of colonic BAs. Through a potential FXR-HP pathway regulatory mechanism, it effectively prevents MASLD. Furthermore, polysaccharide from Dayehuang tea further influences the immunometabolic homeostasis of the gut-liver axis by improving intestinal barrier dysfunction, providing a novel mechanism for dietary intervention in MASLD.

Beyond polysaccharide from Dayehuang tea, other sources of prebiotics also show potential in the treatment of MASLD. A novel polysaccharide, polysaccharides from *Panacis japonici* Rhizoma, extracted from Japanese ginseng significantly reduces the abundance of harmful bacteria, increases the abundance of beneficial bacteria, and improves SCFAs and various metabolic pathways by modulating the gut microbiome, thereby significantly preventing MASLD caused by a HFD.[107] Polysaccharides extracted from *Hericium erinaceus* and Shiitake mushrooms can effectively ameliorate gut microbiota dysbiosis in MASLD, enhance intestinal barrier integrity, restore intestinal redox balance, and alleviate MASLD by regulating the gut-liver axis.[108,109]

Additionally, prebiotics such as Smilacis glabrae polysaccharides, *Arca subcrenata* Lischke polysaccharides, β-glucan supplements from hulless barley, and *Polygonatum sibiricum* polysaccharides exert positive effects on MASLD through different mechanisms.[110-113] They regulate hepatic fat metabolism, repair gut microbiota dysbiosis, increase beneficial bacteria, reduce colonic fat digestion/absorption, and elevate betaine levels, thereby effectively alleviating hepatic steatosis and improving liver function.

The gut-liver axis is a crucial pathway connecting the gut and liver, playing a pivotal role in the pathogenesis of MASLD. Prebiotics (e.g., resistant starch) regulate the gut microbiota structure, improve intestinal barrier function, promote the growth of beneficial bacteria and the production of metabolites, thereby influencing the immunometabolic homeostasis of the gut-liver axis. These metabolites, such as SCFAs and secondary BAs, can directly stimulate the growth of intestinal epithelial cells, triggering G-protein coupled receptor (GPR)41/GPR43, FXR, and Takeda G protein-coupled receptor 5 signaling cascades, thus maintaining the immunometabolic homeostasis in the gut-liver axis and reducing the risk of MASLD.[114] Therefore, prebiotics offer new strategies and directions for the treatment of MASLD by regulating the gut-liver axis.

#### 3) Synbiotics

A synbiotic combination, which utilizes yogurt as the carrier and incorporates probiotics (including *Bifidobacterium* and *Streptococcus thermophilus*) and prebiotics (inulin), has demonstrated significant therapeutic effects in early MASLD animal models.[115] This synbiotic combination can notably improve the levels of TC, TG, and low-density lipoprotein cholesterol (LDL-C) in mice while elevating high-density lipoprotein cholesterol (HDL-C) levels, effectively regulating lipid metabolism. Additionally, it ameliorates IR conditions, further promoting metabolic health. Mechanistically, synbiotics optimize lipid metabolism and alleviate inflammatory responses by activating 5' adenosine monophosphate-activated protein kinase (AMPK) and NF-κB signaling pathways, thereby contributing to the restoration of intestinal barrier function. This effect not only improves the intestinal microenvironment but also significantly alters the composition of the gut microbiota, specifically by reducing the ratio of *Firmicutes* to *Bacteroidetes*, which is of great significance for preventing obesity-related MASLD.

### 2. FMT technology

FMT, as a cutting-edge intestinal microecological intervention strategy, is increasingly gaining attention and being recognized as an innovative approach for MASLD treatment.[116] This technology aims to precisely reconstruct and consolidate the homeostatic balance of the gut microbiota in MASLD patients, thereby optimizing the functional characteristics of the intestinal barrier, particularly improving abnormalities in small intestinal permeability.[117] Through this series of bioregulatory processes, FMT technology is expected to reduce excessive fat accumulation within the liver and effectively inhibit inflammatory responses, thus alleviating the pathological progression of MASLD at a deeper level and providing new perspectives and strategies for the treatment of this complex disease.

The core of FMT technology lies in its full utilization and emphasis on the gut-axis interaction mechanism.[118] Studies have clearly indicated that transferring the fecal microbiota from obese mice with hepatic steatosis to germ-free mice can successfully mimic and recapitulate the typical pathological features of MASLD.[119] Further research has confirmed that FMT technology also exhibits significant therapeutic effects by regulating the gut microbiota balance in NASH patients.[120] Specifically, FMT can improve intestinal permeability, promote the proliferation of beneficial bacteria such as *Clostridia*, and produce metabolites with hepatoprotective effects, such as 4-hydroxyphenylacetic acid. These changes further regulate transcription factors of antioxidant enzymes like nuclear factor erythroid 2-related factor 2 (NRF2) in the liver, effectively reducing the production of inflammatory and fibrotic mediators, thereby significantly improving hepatic fibro-inflammation.

Recently, Chinese researchers conducted a randomized controlled trial comparing FMT with oral probiotics

to further explore the potential of FMT technology.[121] In the trial, participants in the FMT group orally consumed 200 milliliters of fresh bacterial suspension daily for three consecutive days, while the probiotics group received an intervention with *Bifidobacterium* and *Lactobacillus acidophilus* preparations. Both groups adhered to a healthy diet and engaged in more than 40 minutes of exercise daily. Follow-up results after 1 month showed that FMT technology could significantly improve intestinal microbiota dysbiosis and effectively reduce hepatic fat accumulation, with more pronounced therapeutic effects observed in non-obese MASLD patients.

### 3. Targeted drug therapy

Focusing on the role of the gut microbiota and their metabolites in MASLD, based on the gut-liver axis theory, targeted drug therapy is receiving widespread attention as a novel strategy. This strategy aims to regulate microbial homeostasis, improve glucose and lipid metabolism, and alleviate hepatic inflammation and fibrosis through precise pharmacological interventions, thereby optimizing the therapeutic outcomes for MASLD. Herein, a detailed elaboration will be conducted from the two perspectives of Western pharmaceutical science and natural products, respectively.

#### 1) Western medicine

In the therapeutic strategies for MASLD, targeted drug therapy occupies an important position, with Western medications demonstrating significant efficacy. Various Western medications act on the gut-liver axis through different mechanisms, regulating intestinal microbiota and their metabolites, thereby improving the pathological state of MASLD. Of particular note is fenofibrate, a hypolipidemic drug.[122] It primarily acts on the PPARα/peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) signaling pathway to promote mitochondrial β-oxidation, a mechanism that accelerates lipid catabolism and significantly reduces lipid accumulation in the liver. Simultaneously, fenofibrate alleviates oxidative stress damage in the liver, effectively protecting hepatocytes from attack by free radicals and other harmful substances. Furthermore, by activating the PPAR-α/PGC-1α signaling pathway, it promotes mitochondrial biogenesis, not only enhancing the number and function of mitochondria but also increasing ATP production, providing sufficient energy for cells. This process also contributes to improving mitochondrial morphology and function, reducing pathological changes such as excessive fission induced by free fatty acid, thereby playing an important role in the treatment of MASLD.

Additionally, several other Western medications have also demonstrated potential in the treatment of MASLD. For instance, tauroursodeoxycholic acid, a synthetic bile salt, provides additional benefits for MASLD improvement by modulating BAs metabolism, reducing hepatic lipid accumulation, and regulating intestinal microbiota, particularly by increasing the presence of beneficial bacteria, thereby enhancing intestinal barrier function and microbial balance.[123] Nardosinone offers new possibilities for the treatment of MASLD by targeting CYP2D6 and modulating hepatocyte energy metabolism, alleviating oxidative stress damage, as well as regulating the composition of intestinal microbiota.[124] Cilostazol inhibits hepatic lipogenesis through the AMPK-ACC-1/stearoyl-CoA desaturase 1 (SCD1) pathway and suppresses hepatic gluconeogenesis via the AMPK-PGC1α-glucose-6-phosphate/phosphoenolpyruvate carboxykinase pathway. Simultaneously, it regulates intestinal flora and promotes an increase in SCFAs levels, collectively contributing to the restoration of liver health.[125]

Nitidine chloride (NC), within the NC-CS/PT-NPs system, exhibits anti-inflammatory, anti-malarial, and inhibitory properties against hepatocellular carcinoma.[126] Through a colon-targeted delivery system, the interaction between NC and the intestinal microbiota is enhanced, thereby modulating dysbiosis of the intestinal microbiota and exerting a positive effect on MASLD. Lubiprostone is a bicyclic fatty acid compound derived from a prostone metabolite of prostaglandin E1. As a type 2 chloride channel activator and laxative agent, it effectively treats constipation in MASLD patients by improving intestinal permeability, reducing the levels of enzymes related to hepatocyte necrosis, and decreasing endotoxin concentrations.[127] Ferulic acid enhances ileal integrity by activating the nuclear factor E2-related factor 2/heme oxygenase-1 signaling pathway, promotes the production of SCFAs in the colon, and inhibits circulating LPS levels, thereby improving lipid metabolism disorders and reducing hepatic inflammatory responses.[128] Furthermore, PPAR-α agonist WY14643 or/and dipeptidyl peptidase-4 inhibitor linagliptin also demonstrate potential therapeutic effects in the treatment of fatty liver disease in obese mice.[129] Urolithin C, as a potentially active substance, exhibits significant beneficial effects on MASLD by activating the AMPK signaling pathway, inhibiting ferroptosis, regulating intestinal microbiota, and maintaining the intestinal mucosal barrier.[130] Magnesium isoglycyrrhizinate protects against MASLD/NASH by improving intestinal permeability, increasing SCFAs levels in feces, and reducing hepatic oxidative stress and hepatocyte apoptosis.[131]

In summary, Western medicines play a significant role

**Table 1.** Overview of Western Pharmaceuticals for the Treatment of MASLD and Their Mechanisms of Action

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| TUDCA | *In vivo* | Male C57BL/6 mice (HFD) | Oral TUDCA (2.5 mg/kg/day) for 6 wk | *Allobaculum* ↑<br>*Bifidobacterium* ↑ | Promotion (improvement of BAs metabolism) ↑: By influencing the activity of FXR and CYP7A1, it facilitates an elevation in hepatic BAs levels and enhances the expression of NTCP, ultimately leading to an increased concentration of liver-conjugated BAs in mice.<br>Inhibition (reduction of lipid accumulation in the liver) ↓: TUDCA inhibits the expression of FXR and FATP5, thereby decreasing fatty acid absorption and lipid accumulation in the liver. | [123] |
| Nardosinone | *In vivo/ in vitro* | Male C57BL/6N mice (HFD)/HepG2 cell (OA/PA) | 0.18 or 0.36 g/kg nardosinone for 14 wk/50 μM nardosinone for 24 hr | *Escherichia-Shigella* ↓<br>*Enterococcus* ↓<br>*Ruminococcaceae* ↑<br>*UCG-014* ↑<br>*Christensenellaceae* ↑<br>*Alistipes* ↑<br>*Parabacteroides* ↑ | Promotion (amelioration of liver injury and lipid metabolism dysfunction) ↑: Nardosinone ameliorates HFD-induced liver injury and lipid metabolism abnormalities by enhancing mitochondrial energy metabolism in hepatocytes.<br>Inhibition (reduction of oxidative stress damage) ↓: Nardosinone may regulate lipid metabolism by mitigating oxidative stress damage. Furthermore, the binding of nardosinone to CYP2D6 may be involved in its process of regulating lipid metabolism. | [124] |
| Cilostazol | *In vivo* | Male C57BL/6J mice (HFD) | Cilostazol (30, 60, or 120 mg/kg/day) via gavage for 12 wk | *Desulfovibrio* ↓<br>*Akkermansia* ↑ | Promotion (elevation of SCFAs) ↑: Cilostazol promotes an increase in SCFAs levels in MASLD mice, contributing to the improvement of intestinal dysfunction and reduction of hepatic lipid accumulation.<br>Inhibition (suppression of hepatic lipogenesis and hepatic gluconeogenesis) ↓: Cilostazol inhibits hepatic lipogenesis by modulating the AMPK-ACC1/SCD1 pathway, leading to a decrease in hepatic lipid accumulation. Simultaneously, it inhibits hepatic gluconeogenesis through the AMPK-PGC1α-G6P/PEPCK pathway, thereby ameliorating glucose metabolism disorders. | [125] |
| NC (the NC-CS/PT-NPs were synthesized using the ion gel method) | *In vivo* | Male C57 mice (HFD) | Containing NC 8 mg/kg/day, by gavage for 4 wk | *Firmicutes*-to-*Bacteroidetes* ratio ↑<br>*Desulfobacterota* ↓<br>*Campylobacterota* ↓<br>*Deferribacteres* ↓<br>*Oscillospirales* ↓<br>*Campylobacterales* ↓<br>*Alloprevotella* ↑ | Inhibition (reduction of serum enzymes and lipid levels) ↓: NC-CS/PT-NPs treatment inhibits weight gain, decreases serum enzyme levels (AST and ALT), and lipid levels in mice, ameliorates liver and intestinal inflammation, and alters gut microbiota diversity. | [126] |
| Fenofibrate | *In vivo/ in vitro* | Male C57BL/6J mice (HFD)/HepG2 cells (FFA) | 0.04 g/kg/day fenofibrate by gavage for 4 wk/lentivirus LV-PPARGC1A ($2\times10^8$ TU/mL) for 72 hr | | Promotion (PPARα/PGC-α) ↑: Enhances mitochondrial ß-oxidation, alleviates hepatic oxidative stress damage, promotes mitochondrial biogenesis, and increases ATP production.<br>Inhibitory (lipid accumulation and oxidative stress) ↓: Inhibits lipid accumulation and oxidative stress. | [122] |
| Lubiprostone (bicyclic fatty acid compound) | *Clinical trial* | Patients (aged 20–85 yr) with MASLD and constipation | 12 or 24 μg of lubiprostone orally once daily for a duration of 12 wk | | Inhibitory (improving intestinal permeability, reducing ALT and endotoxin levels) ↓: Lubiprostone not only ameliorates the critical pathological indicator of intestinal permeability but also effectively decreases the levels of hepatocyte necrosis-associated enzyme (ALT) and mitigates the concentration of endotoxin in the bloodstream. | [127] |

**Table 1.** Continued

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Ferulic acid | *In vivo* | Male C57BL/6J mice (HFD) | 40 mg/kg FA orally for 6 wk | *Enterococcus* ↑<br>*Streptococcus* ↑<br>*Prevotella* ↑<br>*[Ruminococcus]* ↑<br>*_gnavus_group* ↑<br>*Alloprevotella* ↑<br>*Faecalibacterium* ↑<br>*Terrisporobacter* ↑<br>*Helicobacter* ↓<br>*Mucispirillum* ↓<br>*Romboutsia* ↓ | Promotion (improvement of ileal intestinal integrity, increase in colonic SCFAs levels) ↑: Enhancement of ileal intestinal integrity through the Nrf2/HO-1 signaling pathway, facilitating the production of SCFAs in the colon, which in turn induces the activation of NF-κB and p38MAPK signaling pathways via GPR43.<br>Inhibition (amelioration of lipid metabolic disorder, reduction of hepatic inflammatory response) ↓: Suppression of circulating LPS levels, thereby decreasing systemic LPS levels and inhibiting the hepatic TLR4 signaling pathway. | [128] |
| PPARα agonist WY14643 or/and DPP-4 inhibitor linagliptin | *In vivo* | Male C57BL/6J mice (HFD) | WY14643 (2.5 mg/kg body mass) or/and linagliptin (15 mg/kg body mass) | *Bacteroidetes-Firmicutes* ratio ↑ | Promotion (of intestinal barrier function recovery) ↑: It can significantly impact the gut microbiota, increasing the number of goblet cells per area in the large intestine and reducing lipopolysaccharide concentrations, while enhancing the expression of Mucin 2, Occludin, and ZO-1 genes.<br>Inhibition (of hepatic steatosis) ↓: It blocks the endotoxinemia and the expression of inflammasome and macrophage genes in the liver, thereby reducing hepatic TG levels. | [129] |
| UroC | *In vivo*/ *In vitro* | Male C57BL/6J mice (choline-deficient amino acid-defined HFD)/AML12 cell (oleic acid) | Gavaged by UroC (40 mg/kg/day) for 4 wk/100 μM UroC for 48 hr | *Firmicutes-Bacteroidota* ratio ↑<br>*Parabacteroides goldsteinii* ↑<br>*Lactobacillus vaginalis* ↑ | *In vivo* experiments: The AMPK signaling pathway in the liver was activated (promoting the AMPK signaling pathway), which is believed to inhibit the ferroptosis response to UroC *in vivo*.<br>*In vitro* experiments: The AMPK-ferroptosis axis in oleic acid-induced AML12 cells exhibited no change in response to UroC, suggesting an indispensable link between UroC and hepatic AMPK, potentially acting through the gut-liver axis. | [130] |
| MgIG | *In vivo* | Male C57BL/6 mice (HFD and 1% dextran sulfate sodium) | MgIG (30 or 60 mg/kg) by gavage for 7 wk | | Promotion (improvement of intestinal permeability) ↑: By increasing the levels of SCFAs in feces, there is an improvement in serum biochemistry.<br>Inhibition (reduction of hepatic steatosis and fibrosis) ↓: By decreasing hepatic oxidative stress and hepatocyte apoptosis. | [131] |

MASLD, metabolic dysfunction-associated steatotic liver disease; TUDCA, tauroursodeoxycholic acid; HFD, high-fat diet; BAs, bile acids; FXR, farnesoid X receptor; CYP7A1, 7α-hydroxylase; NTCP, sodium taurocholate cotransporting polypeptide; FATP5, fatty acid transport protein 5; SCFAs, short-chain fatty acids; AMPK, 5' adenosine monophosphate-activated protein kinase; ACC1, acetyl-CoA varboxylase 1; SCD1, stearoyl-CoA desaturase 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; G6P, glucose-6-phosphate; PEPCK, phosphoenolpyruvate carboxykinase; NC-CS, nitidine chloride-chitosan; PT-NPs, pectin-targeted nanoparticles; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FFA, free fatty acid; PPAR, peroxisome proliferator-activated receptor; FA, ferulic acid; Nrf2, nuclear factor E2-related factor 2; HO-1, heme oxygenase-1; NF-κB, nuclear factor kappa-B; p38MAPK, p38 mitogen-activated protein kinase; GPR43, G protein-coupled receptor 43; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; DPP-4, dipeptidyl peptidase 4; TG, triglycerides; UroC, urolithin C.

in the treatment of MASLD, particularly drugs like fenofibrate, which have opened up new avenues for MASLD treatment by acting on the gut-liver axis and modulating the intestinal microbiota and their metabolites. For specific mechanisms of drug action and details, please refer to Table 1.

### 2) Natural products

#### (1) Single compounds

In the therapeutic strategies for MASLD, natural products have emerged as a pivotal branch of targeted drug therapy, exhibiting broad application prospects. Among them, various single compounds exert positive effects on MASLD treatment by modulating the gut microbiota and their metabolites. Of particular note is icariin, a promising active ingredient, which demonstrates significant efficacy in treating MASLD.[132] Icariin mediates the regulation of NF-κB and MAPK pathways by upregulating the expression of miR-206 in liver tissues and cells. This regulatory effect not only promotes the synthesis and secretion of HDL-C, improves lipid metabolism, and reduces abnormal lipid accumulation in the liver, but also decreases the levels of multiple biochemical markers in serum, such as ALT, AST, total bilirubin, TG, TC, and LDL-C, by inhibiting the excessive activation of NF-κB and MAPK pathways. The reduction of these markers directly reflects the alleviation of liver tissue damage and the decrease in lipid deposition. Furthermore, icariin effectively lowers the levels of inflammatory cytokines (e.g., IL-1β, IL-12, and IL-6) in liver tissues and cells by inhibiting the NF-κB and MAPK pathways, thereby mitigating the MASLD-related inflammatory response and further protecting the liver from damage. Icariin, as a single compound derived from natural products, provides important theoretical and practical guidance for the clinical application in MASLD.

In addition to icariin, other single compounds derived from natural products have also demonstrated therapeutic potential for MASLD. For instance, rutin, a biologically active flavonoid compound, exhibits significant therapeutic potential for MASLD by activating the AMPK signaling pathway, inhibiting the SREBP1 pathway, and modulating the gut microbiota structure, particularly by significantly reducing the ratio of *Firmicutes* to *Bacteroidetes*.[133] *Zanthoxylum bungeanum* amides, a potential active substance of pepper amides, show remarkable improvement in MASLD by regulating the composition and structure of the intestinal microbiota (e.g., increasing beneficial bacteria such as *Bacteroides* and *Akkermansia*, and reducing harmful bacteria like *Olsenella*), and activating the AMPK/Nrf2 signaling pathway.[134] Ginsenoside Rg5, by activating the liver kinase B1/AMPK/mammalian targets of rapamycin (LKB1/AMPK/mTOR) signaling pathway and modulating the gut microbiota, alleviates liver injury and demonstrates significant therapeutic potential in improving MASLD.[135]

Furthermore, punicic acid in pomegranate seed oil has demonstrated potential in improving obesity-related hyperlipidemia and fatty liver disease through multiple mechanisms, including antioxidant, anti-inflammatory effects, and modulation of the gut microbiota.[136] Thyme polyphenol-rich extract from *Thymus quinquecostatus* Celak effectively alleviates hepatic steatosis induced by a HFD by regulating the gut microbiota, promoting bile acid excretion, and modulating the expression of genes related to BAs metabolism.[137] Polyphenol extract from *Prunus cerasifera* Ehrhart in the arid landscapes of Xinjiang, China, which is a potential active polyphenol component in cherry trees, exhibits therapeutic effects on MASLD through multiple mechanisms, including promoting the synthesis of hepatic BAs, enhancing cholesterol efflux in the intestine, and regulating the balance of beneficial gut microbiota.[138] Bound polyphenols from foxtail millet, as a potential active substance, play a significant role in the treatment of MASLD by modulating the intestinal microbiota, enhancing intestinal barrier function, and improving lipid metabolism and inflammation.[139] Tanshinone IIA and its derivatives, as potential active substances in *Salvia miltiorrhiza* Bge, effectively alleviate MASLD by activating transcription factor EB to promote lysosomal biogenesis, improving the expression of genes related to lipid metabolism, and regulating gut microbiota homeostasis.[140]

#### (2) Extracts containing multiple compounds

In the treatment of MASLD, various extracts containing multiple compounds have also demonstrated significant efficacy, primarily by modulating the structure of intestinal microbiota and their metabolites. For instance, Tangshen formula (consisting of astragalus root, burning bush twig, rehmannia root, bitter orange, cornus fruit, rhubarb root and rhizome, and notoginseng) effectively intervenes in MASLD by adjusting intestinal microbiota and optimizing the metabolic profile. It thereby rationally regulating multiple beneficial bacterial species, maintaining intestinal microecological balance, and subsequently improving liver metabolic function and reducing the production of differential metabolites closely associated with MASLD improvement.[141] Components such as tea polyphenols and tea polysaccharides in chin brick tea extracts regulate intestinal microbiota and metabolites, increasing the levels of beneficial bacteria and decreasing the number of harmful bacteria, optimizing BAs metabolism (such as deoxycholic acid and ω-Muricholic acid), and inhibiting the production of inflammatory cytokines (such as IL-1β and IL-18) and

adverse metabolites, thereby achieving effective treatment for MASLD.[142]

The bioactive components of hawthorn in Hawthorn Ethanol Extract, which primarily include organic acids and flavonoids such as citric acid, hawthorn acid, caffeic acid, catechins, quercetin, hyperoside, and apigenin 8-C-glucoside, exhibit multiple effects, including lipid-lowering properties, modulation of intestinal microbiota, and anti-inflammatory activities. These components effectively treat MASLD through mechanisms involving the promotion of TG catabolism, inhibition of fatty acid synthesis, regulation of intestinal microbial diversity, and enhancement of SCFAs production.[143] On the other hand, Ling-Gui-Zhu-Gan decoction (Fulin, Guizhi, Baizhu, Gancao) significantly improves the pathological state of MASLD through various mechanisms including increasing intestinal SCFAs concentrations, restoring disordered BAs metabolism, and mediating PPAR signaling pathways. The active ingredients of Ling-Gui-Zhu-Gan decoction primarily originate from multiple Chinese herbal medicines.[144]

Zexie-Baizhu Decoction (composed of *Alisma orientalis* (Sam.) Juzep. and *Atractylodes macrocephala* Koidz) regulates the composition of intestinal microbiota through its active ingredients, particularly by increasing the number of *Akkermansia muciniphila*, adjusting the ratio of *Firmicutes* to *Bacteroidetes*, and modulating the levels of BAs and SCFAs, as well as their receptor activation (e.g., Gpbar1 and FFAR2). These effects influence the expression of related genes and alter liver lipid composition, thereby effectively treating MASLD.[145] Additionally, a combination of silymarin, salvianolic acid B, and puerarin significantly improves MASLD symptoms by regulating intestinal microbiota structure, increasing probiotics, inhibiting harmful bacteria, and affecting BAs metabolism.[146]

Additionally, Qushi Huayu (a traditional Chinese medicinal formula for removing dampness and resolving blood stasis), composed of Yin Chen, Hu Zhang, Tian Jihuang, Jiang Huang, and Zhi Zi, has demonstrated significant efficacy in the treatment of MASLD by modulating the gut microbiota structure, influencing related microbial metabolites (such as reducing peripheral blood levels of phenylalanine and tyrosine, and increasing levels of 4-hydroxyphenylacetic acid), decreasing hepatic fat content, and elevating ALT levels.[147] Zuogui Jiangtang Qinggan Fang exhibits notable effects in the treatment of type 2 diabetes complicated with MASLD. Its mechanism involves regulating the gut microbiota and the composition of metabolic products SCFAs, upregulating the expression of liver fatty acid oxidation-related genes (e.g., PGC-1, PPAR-α, and UCP1), enhancing intestinal barrier function, and precisely regulating the concentrations of

**Table 2.** Overview of Natural Products for the Treatment of MASLD and Their Mechanisms of Action

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Single compounds | | | | | | |
| Rutin | *In vivo*/*in vitro* | Male C57BLKs/J-db/db (db/db) or C57BLKs/J-db+/+m (db/m) mice (purchased)/HepG2 cell (OA or d-glucose and PA) | Rutin = 100 or 200 mg/kg/day for 8 wk | *Firmicutes-Bacteroidetes* ratio ↓ | Promotion (of AMPK) ↑: Rutin promotes the activation of the AMPK pathway.<br>Inhibition (of SREBP1) ↓: Rutin inhibits lipid synthesis through the SREBP1 pathway. | [133] |
| *Zanthoxylum bungeanum* amides (AZB) | *In vivo* | Male C57BL/6J mice (HFD) | AZB (5, 10, or 20 mg/kg) for 12 wk | *Allobaculum* ↑<br>*Bacteroides* ↑<br>*Dubosiella* ↑<br>*Firmicutes-Bacteroidota* ratio ↓ | Promotion (activation of AMPK/Nrf2 signaling) ↑: By increasing the abundance of SCFAs-producing bacteria, upregulating AMPK phosphorylation, and enhancing Nrf2 nuclear transcription, the AMPK/Nrf2 signaling pathway is activated, thereby alleviating oxidative stress and improving liver function.<br>Inhibition (reduction in the *Firmicutes-Bacteroidetes* ratio) ↓: By modulating the composition and structure of the gut microbiota. | [134] |

**Table 2.** Continued 1

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Ginsenoside Rg5 (Rg5) | *In vivo* | Male C57BL/6J mice (HFD) | Rg5 (50 or 100 mg/kg/day) for 12 wk | *Bacteroides* ↑<br>*Akkermansia*↑<br>*Olsenella* ↓ | Promotion (of energy metabolism) ↑: Activation of the LKB1/AMPK/mTOR signaling pathway enhances energy metabolism and modulates the gut microbiota.<br>Inhibition (of liver injury) ↓: Significant improvement in biochemical parameters and alleviation of liver injury in MASLD mice induced by a HFD. | [135] |
| Punicic acid (mainly found in pomegranate seed oil) | *In vivo* | Male C57BL/6J mice (a high-fructose HFD) | 2% pomegranate seed oil for 13 wk | *Muribaculaceae* ↑<br>*Blautia* ↓ | Promotion (of antioxidant capacity) ↑: Enhancement of T-AOC and SOD activities, as well as GSH levels, coupled with a reduction in MDA content in the liver, mitigates oxidative stress, restores normal levels of the anti-inflammatory cytokine IL-10, and elevates SCFAs levels.<br>Inhibition (of TLR4/MyD88/NF-κB and TLR4/IL-22/STAT3 pathways) ↓: Suppression of the activation of TLR4/MyD88/NF-κB and TLR4/IL-22/STAT3 signaling pathways in the liver inhibits the expression of pro-inflammatory mediators (IL-6 and IL-1ß). | [136] |
| Thyme polyphenol-rich extract (TPE) (from *Thymus quinquecostatus* Celak) | *In vivo* | Male C57BL/6J mice (HFD) | 400 mg $kg^{-1}$ TPE through daily intragastric gavage for 8 wk | *Lactobacillus* ↑ | Promotion (facilitating BAs excretion and enterohepatic circulation) ↑: modulating the intestinal microbiota, enhancing fecal BAs excretion, upregulating the expression of hepatic BAs synthetic enzymes Cyp7a1 and Cyp27a1, and promoting BAs excretion and enterohepatic circulation.<br>Inhibition (mitigating hepatic steatosis) ↓: Reducing serum total BAs levels, downregulating the expression of intestinal Fxr and hepatic Fgfr4, effectively mitigating hepatic steatosis. | [137] |
| Polyphenol extract (PPE) (from *Prunus cerasifera* Ehrhart in the arid landscapes of Xinjiang, China) | *In vivo* | ICR mice (HFD) | PPE (200 or 400 mg/kg/day, BW) for 11 wk | *Turicibacter* ↑<br>*Lactobacillus* ↑<br>*Candidatus_Saccharimonas*↑<br>*Parabacteroides*↑<br>*Akkermansia* ↑<br>*Neglecta* ↑ | Promotion (enhancing liver BAs synthesis, intestinal cholesterol efflux, and BAs secretion) ↑: Upregulation of CYP7A1 and CYP27A1 expression; upregulation of LXRα, ABCA1, ABCG5, and ABCG8 expression; facilitation of BAs secretion via BSEP.<br>Inhibition (suppressing liver cholesterol synthesis, intestinal cholesterol absorption, and BAs secretion) ↓: Reduction in HMGCR activity; decrease in ACAT2 levels; indirect downregulation of BAs secondary metabolites (DCA and LCA) under the influence of lipotoxic BAs. | [138] |
| Bound polyphenols from foxtail millet (BPIS) | *In vivo* | Male C57BL/6N mice (HFD) | BPIS (100 mg $kg^{-1}$) by gavage treatment for 12 wk | *Firmicutes*↑<br>*Allobaculum* ↑<br>*Lactobacillus* ↑<br>*Ruminococcus genus*↑<br>*Bacteroidetes* ↓ | Promotion (tight junction protein expression) ↑: Upregulation of ZO-1, Claudin, and Occludin.<br>Inhibition (lipid metabolism and inflammation) ↓: Activation of AMPK and NF-κB signaling pathways leads to improvements in biochemical substances such as TG and TC, alters lipid metabolism and inflammation, and addresses intestinal barrier dysfunction and inflammation induced by HFD. | [139] |

**Table 2.** Continued 2

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Tanshinone IIA and derivatives derived from Salvia miltiorrhiza Bge (SMB) | *In vivo* | Male C57BL/6J mice (HFD) | 9 or 15 g/kg (w/w) of SMB per day for 8 wk | *Bacteroidota* ↑<br>*Verrucomicrobiota*↑<br>*Firmicutes* ↓<br>*Actinobacteriota* ↓ | Promotion (restoration of lipid metabolism-related genes) ↑: Induction of lysosomal biogenesis to facilitate the restoration of Lpin1, Acsl3, Hmgcr, and Cidea gene expression.<br>Inhibition (metabolic disorders associated with fatty degeneration) ↓: Inhibition of LPIN1, ACSL3, HMGCR, and CIDEA protein expression to ameliorate IR. | [140] |
| Icariin | *In vivo/ in vitro* | Male SD rats (HFD)/ HepG2 cells (free fatty acid) | 25, 50, or 75 mg/kg ICA ICA, for 10 wk/ 20, 40, or 80 μM ICA for 24 hr | | Promotion (miR-206) ↑: By upregulating the expression of miR-206, it enhances HDL-C levels, ameliorates hepatic tissue damage, and reduces lipid deposition.<br>Inhibition (NF-κB and MAPK) ↓: By inhibiting the activation of NF-κB and MAPK pathways, it decreases the levels of serum biochemical indicators (ALT, AST, TBil, TG, TC, LDL-C), improves hepatic tissue damage and lipid deposition, and reduces the levels of inflammatory cytokines (IL-1β, IL-12, IL-6) in liver tissues and cells. | [132] |
| Extracts containing multiple compounds | | | | | | |
| *Tangshen formula* (TSF) (astragalus root, burning bush twig, rehmannia root, bitter organge, cornus fruit, rhubarb root and rhizome, and notoginseng) | *In vivo* | Male C57BL/6J mice (HFD) | TSF (3.6g/kg/day) for 1 wk | *Atopobiaceae* ↑<br>*Faecalibaculum*↑<br>*Sporosarcina*↑<br>*Lachnospiraceae*↑<br>*Bifidobacterium*↑<br>*Eggerthellaceae* ↑ | Promotion (reshaping intestinal microbiota) ↑: By reshaping the gut microbiota, it significantly increases the abundance of beneficial bacteria and decreases the proportion of harmful bacteria.<br>Inhibition (mitigating harmful metabolic pathways) ↓: It mitigates the production of 172 differential metabolites closely related to MASLD improvement, particularly the metabolic pathways of choline, glycerophospholipids, linoleic acid, α-linolenic acid, and arachidonic acid. | [141] |
| CBT (contain mainly tea polyphenols, free amino acids, caffeine, catechins, tea polysaccharides, and other components) | *In vivo* | Male C57BL/6 mice (HFD) | 75 or 300 mg $kg^{-1}$ of aqueous extract of CBT by gavage for 14 wk | *Lactobacillus* ↑<br>*Alloprevotella* ↑<br>*Ruminococcaceae*↑<br>*Bacteroides* ↓ | Promotion (modulation of gut microbiota structure and metabolites) ↑: By increasing the levels of *Lactobacillus*, *Alloprevotella*, and *Ruminococcaceae*, while decreasing the level of *Bacteroides*. Additionally, it elevates the ratio of primary to secondary BAs.<br>Inhibition (reduction of inflammatory cytokines and production of adverse metabolites) ↓: CBT significantly decreases the levels of IL-1β and IL-18, and inhibits the proliferation of BAs such as DCA and ωMCA, as well as harmful gut microbiota such as *Bacteroides*. | [142] |

**Table 2.** Continued 3

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Hawthorn ethanol extract (HEE) (contain mainly organic acids and flavonoids, citric acid, hawthorn acid, caffeic acid, catechins, quercetin, hyperoside, and apigenin 8-C-glucoside) | *In vivo* | Male C57BL/6/J mice (HFD) | 150 mg/kg HEE for 16 wk | *Bacteroidetes*↑<br>*Bacteroidetes-Firmicutes* ratio↑<br>*Lactobacillus*↑<br>*Lachnospiraceae [Eubacterium] fissicatena group*↑<br>*Ruminiclostridium 9*↑<br>*Romboutsia* ↑<br>*Stenotrophomonas maltophilia* ↓<br>*Enterobacteriaceae* ↓ | Promotion (increasing SCFAs production and promoting TG breakdown) ↑: By modulating the production of SCFAs in the gut, intestinal health is enhanced. Additionally, promoting TG breakdown and inhibiting fatty acid synthesis contribute to improving hepatic lipid accumulation.<br>Inhibition (suppressing inflammatory cytokines) ↓: By suppressing the production of inflammatory cytokines (TNF-$\alpha$, IL-6, LBP, and LPS), it reduces blood lipid levels and regulates blood glucose levels. | [143] |
| Ling-Gui-Zhu-Gan decoction (LG) (Fulin, Guizhi, Baizhu, Gancao) | *In vivo* | Male C57BL/6 mice (HFD) | 715 mg/kg/day LG intragastrically once daily for 8 wk | *Lactobacillus* ↑<br>*Alistipes putredinis* ↑<br>*Porphyromonadaceae*↑<br>*Mogibacteriaceae* ↑<br>*Peptococcaceae* ↓<br>*Odoribacter* ↓ | Promotion (increasing SCFAs concentration) ↑: Enhances the improvement of intestinal barrier function by increasing the concentration of SCFAs in feces.<br>Inhibition (reducing BAs and mediating PPAR) ↓: Inhibits the gene expression related to the biosynthetic pathway of primary BAs and downregulates the expression of CYP7A1/FXR in the liver, thereby restoring BAs metabolism disorders and mediating the PPAR signaling pathway to reduce lipogenesis and alleviate liver inflammation. | [144] |
| Zexie-Baizhu Decoction (AA) (Alisma orientalis (Sam.) Juzep. and Atractylodes Macrocephala Koidz) | *In vivo* | Male C57BL/6J mice (HFD) | AA (1,500 mg/kg/day) for 29 wk | *Akkermansia muciniphila*↑<br>*Firmicutes-Bacteroidetes* ratio↑ | Promotion (increasing SCFAs and activating FFAR2) ↑: By elevating SCFAs levels in the intestine, plasma, and liver, thereby activating the SCFAs receptor (FFAR2) in eWAT. This activation influences the expression of genes related to fatty acid metabolism, thermogenesis, IR, AMPK signaling, and TCA cycle at the transcriptomic level. Additionally, it alters the lipid composition in the liver by decreasing the levels of diacylglycerols, triacylglycerols, phosphatidylserines, and cholesterol esters, while increasing the levels of phosphatidic acids, phosphatidylethanolamines, and sphingomyelins.<br>Inhibition (reducing BAs and activating Gpbar1) ↓: By reducing BAs levels in the intestine, plasma, and liver, resulting in the activation of the BAs receptor (Gpbar1) in eWAT. This activation also influences the expression of genes at the transcriptomic level and modifies the lipid composition in the liver. | [145] |

**Table 2.** Continued 4

| Drug | Study type | Experimental subject | Experimental design | Modulation target (gut microbiota structure) | Modulation target (mechanism) | Reference |
|---|---|---|---|---|---|---|
| Supplementation of silymarin alone or in combination with salvianolic acids B and puerarin | *In vivo* | Male C57BL/6J mice (HFD) | 0.101 or 0.202 g silymarin; supplemented with polyherbal extract (0.101 g silymarin, 0.046 g salvianolic acid B, 0.042 g Puerarin). (according to the dietary intake of 0.1 g/g·bw·day) for 16 wk | *Akkermansia*↑<br>*Blautia*↑<br>*Clostridium* ↓ | Promotion (of modulating intestinal microbiota) ↑ and Inhibition (of BAs metabolism) ↓: silymarin, salvianolic acid B, and puerarin significantly ameliorate MASLD induced by HFD in mice by modulating intestinal microbiota and their metabolites (impacting BAs metabolism), thereby restoring liver function. | [146] |
| Qushi Huayu (QSHY) (Yin Chen, Hu Zhang, Tian Jihuang, Jiang Huang, and Zhi Zi) | Clinical trial | Patients with MASLD and liver dysfunction | QSHY granules (5.2 g, b.i.d.) for 24 wk | *Bacteroides* ↑<br>*Escherichia* ↓<br>*Shigella*↓ | Promotion (modulation of gut microbiota structure) ↑: By modulating the gut microbiota structure, it subsequently influences related microbial metabolites, such as reducing peripheral blood levels of phenylalanine and tyrosine, and increasing levels of 4-hydroxyphenylacetic acid.<br>Inhibition (reduction of liver fat) ↓: It decreases liver fat content, improves ALT levels, aspartate aminotransferase levels, and Fibrosis-4 scores. | [147] |
| Zuogui Jiangtang Qinggan Fang (ZGJTQGF) | *In vivo* | MKR transgenic mice (HFD) | ZGJTQGF therapy group (7.5 or 15 $g \cdot kg^{-1}$) by gavage for 8 wk | *Bacteroidota* ↑<br>*Lactobacillus* ↑<br>*Akkermansia*↑<br>*Firmicutes* ↓<br>*Desulfobacterota* ↓<br>*Proteobacteria* ↓<br>*Bacteroidota-Firmicutes* ratio↓ | Promotion (increase in SCFAs and intestinal barrier indices) ↑: Elevated levels of SCFAs, with upregulated expression of liver fatty acid oxidation-related genes (PGC-1, PPAR-α, UCP1). Enhanced expression of intestinal barrier indices ZO-1, occludin, and claudin-1.<br>Inhibition (hepatic lipid accumulation and IR) ↓: Improved dyslipidemia, with reduced accumulation of hepatic lipids and glycogen. Suppressed expression of fat-generating related genes (SREBP-1c, CD36, SCD1, LXR). Modulated levels of specific metabolites in liver tissue, including L-glutamic acid, L-phenylalanine, glycine, taurine, deoxycholic acid, and citric acid. | [148] |

MASLD, metabolic dysfunction-associated steatotic liver disease; OA, oleic acid; PA, palmitic acid; AMPK, 5' adenosine monophosphate-activated protein kinase; Fxr, Farnesoid X Receptor; SREBP1, sterol regulatory element-binding protein 1; HFD, high-fat diet; rf2, nuclear factor E2-related factor 2; SCFAs, short-chain fatty acids; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; T-AOC, total antioxidant capacity; SOD, superoxide dismutase; GSH, glutathione; MDA, malondialdehyde; IL, interleukin; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3; BAs, bile acids; CYP7A1, 7α-hydroxylase; BSEP, bile salt export pump; ACAT2, acetyl-CoA acetyltransferase 2; DCA, deoxycholic acid; LCA, lithocholic acid; TG, triglycerides; TC, total cholesterol; IR, insulin resistance; HDL-C, high-density lipoprotein cholesterol; MAPK, mitogen-activated protein kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, total bilirubin; LDL-C, low-density lipoprotein cholesterol; CBT, chin brick tea; ωMCA, ω-Muricholic acid; TNF, tumor necrosis factors; LBP, lipopolysaccharide binding protein; LPS, lipopolysaccharide; PPAR, peroxisome proliferator-activated receptor; FXR, farnesoid X receptor; FFAR, free fatty acid receptor; eWAT, epididymal white adipose tissues; TCA, tricarboxylic acid.

specific metabolites in liver tissue (including L-glutamic acid, L-phenylalanine, glycine, taurine, deoxycholic acid, and citric acid), effectively inhibiting the expression of fat generation-related genes (such as SREBP-1c, CD36, SCD1, and LXR).[148]

In summary, natural products including both single compounds and extracts containing multiple compounds have demonstrated significant therapeutic efficacy in the treatment of MASLD. Notably, natural products derived from single compounds such as icariin, as well as those from extracts containing multiple compounds, show great potential in treating MASLD by regulating the gut-liver axis and influencing the balance of intestinal microbiota and their metabolites. For specific mechanisms of action and detailed information on these drugs, please refer to Table 2.

Targeted drug therapy, whether derived from Western medicines or natural products, has demonstrated promising therapeutic potential as a crucial component of MASLD treatment strategies. In the future, with deeper insights into the pathogenesis of MASLD and the interactions between the gut microbiota and the host, targeted drug therapy will become more precise and effective, offering MASLD patients superior therapeutic outcomes.

## CONCLUSIONS

The gut microbiota and its metabolites play pivotal roles in the progression of MASLD. Through the gut-liver axis regulatory mechanism, imbalances in the gut microbiota and abnormalities in metabolites not only promote the onset and progression of MASLD but also exhibit unique characteristics and changes in patients with cirrhosis and its complications. Specifically, significant alterations occur in the composition of the gut microbiome in cirrhotic patients, which are closely associated with the presence of complications, thus uncovering the potential utility of the gut microbiota as diagnostic biomarkers. Concurrently, fecal metabolites such as SCFAs and indoles have also demonstrated potential as diagnostic and prognostic biomarkers.[149] These findings not only provide valuable insights into understanding the role of gut microbiota and metabolites in the progression of MASLD and cirrhosis but also emphasize that therapeutic strategies targeting the gut microbiota and its metabolites offer novel treatment avenues for MASLD. Therefore, future research will further explore the interaction mechanisms between the gut microbiota and related diseases, validate the effectiveness of these biomarkers, and develop more effective treatment modalities to improve patient prognosis and quality of life.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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